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Age at menarche and adult body mass index: a Mendelian randomization study

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DG, FDGM and CM had access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

DG affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Abstract

Background: Pubertal timing has psychological and physical sequelae. While observational studies have demonstrated an association between age at menarche and adult body mass index (BMI), confounding makes it difficult to infer causality.

Methods: The Mendelian randomization (MR) technique is not limited by traditional confounding and was used to investigate the presence of a causal effect of age at menarche on adult BMI. MR uses genetic variants as instruments under the assumption that they act on BMI only through age at menarche (no pleiotropy). Using a two-sample MR approach, heterogeneity between the MR estimates from individual instruments was used as a proxy for pleiotropy, with sensitivity analyses performed if detected. Genetic instruments and estimates of their association with age at menarche were obtained from a genome-wide association meta-analysis on 182,416 women. The genetic effects on adult BMI were estimated using data on 80,465 women from the UK Biobank. The presence of a causal effect of age at menarche on adult BMI was further investigated using data on 70,692 women from the GIANT Consortium.

Results: There was evidence of pleiotropy among instruments. Using UK Biobank data, after removing instruments associated with childhood BMI that were likely exerting pleiotropy, fixed-effect meta-analysis across instruments demonstrated that a one year increase in age at menarche reduces adult BMI by 0.38kg/m^2 (95%CI 0.25 to 0.51kg/m^2). However, evidence of pleiotropy remained. MR-Egger regression did not suggest directional bias, and similar estimates to the fixed-effect meta-analysis were obtained in sensitivity analyses when using a random-effect model, MR-Egger regression, a weighted median estimator and a weighted mode-based estimator. The direction and significance of the causal effect were replicated using data from the GIANT Consortium.

Conclusion: MR provides evidence to support the hypothesis that earlier age at menarche causes higher adult BMI. Complex hormonal and psychological factors may be responsible.

Abstract Word count: 300

Key words: Mendelian randomization, puberty, menarche, body mass index, obesity

Introduction

Following current trajectories, almost one fifth of the global population will be obese by 2030 (1), emphasising the importance of understanding predisposing factors for obesity. Pubertal timing has come under increasing attention due to the associated psychological and physical sequelae (2, 3), and early menarche in particular has been shown to be a risk factor for eating disorders (4), depression (5), type 2 diabetes (6), cardiovascular disease and mortality (7). Earlier pubertal timing in girls has been associated with higher body mass index (BMI) in adulthood (3). However, childhood obesity is a risk factor for adult obesity, and adjusting for this variable has resulted in inconsistent effect estimates of the association between pubertal timing and adult BMI, ranging from a modest reduction of adult BMI with delayed pubertal timing (8-10), to complete loss of statistical evidence (11). Thus, it is difficult to decipher whether age at menarche indeed has a causal effect on adult obesity, or whether the association is wholly attributable to confounding factors that also affect the timing of menarche, such as pubertal adiposity or individual socio-economic factors (10, 12).

The Mendelian randomization (MR) technique uses genetic variants as instruments ("proxies") for a risk factor of interest, which here is age at menarche. As these genetic variants are allocated randomly at the time of conception, MR may be used in this situation to disentangle a causal effect of age at menarche on adult BMI from spurious associations attributable to confounding (13). Indeed, this approach has recently been used to demonstrate causal effects of age at menarche on adolescent depression (14), time spent in education (15), adolescent and adult lung function (16), and risk of breast cancer and endometrial cancer (17). A critical assumption of MR analysis is that the instrumental variables do not affect the outcome via a pathway other than the risk factor of interest. Genetic variants can violate this assumption if they exert their effects on the outcome through different biological pathways in a phenomenon known as horizontal pleiotropy (18). Although there are methods that address horizontal pleiotropy, these must be carefully selected and appropriately interpreted because they vary in their underlying assumptions and power to identify a causal effect (19, 20). Indeed, while recent work has used MR to suggest that higher age at menarche results in lower adult BMI, causal effect estimates and possible bias resulting from horizontal pleiotropy were not explored in this analysis (17).

In this study, we use a two-sample MR approach with single nucleotide polymorphism (SNP)-age at menarche and SNP-adult BMI association estimates to investigate the causal effect of age of menarche on adult BMI. We also perform sensitivity analyses that address the issue of horizontal pleiotropy and assess the robustness of the findings.

Materials and Methods

A published genome-wide association (GWA) meta-analysis of 57 studies incorporating 182,416 women was used to identify SNPs for use as instruments for age at menarche, and to obtain estimates of the magnitude of their association (21). Onset of menarche was established from questionnaires, with analysis adjusted for birth year (for secular trends) and genomic control (for population stratification). A total of 122 independent SNPs situated at 106 genomic loci were identified to be associated with age at menarche at genome-wide significance level (p value $< 5 \times 10^{-8}$). We calculated

the F statistic of each SNP, which reflects magnitude and precision of the genetic effect, to evaluate its strength as an instrument (22, 23).

SNP-adult BMI association estimates for each of the 122 instruments were obtained from the UK Biobank, a prospective study performed across 22 assessment centres (24). We include 80,465 women aged 40-69 recruited in 2006–2010, who had BMI (kg/m², calculated using height and weight measurements) and GWA data available. Analyses were adjusted for age, age^2, 10 ancestry principal components and study centre.

The presence of a causal effect of age at menarche on adult BMI was further investigated using SNP-adult BMI summary data made publicly available by the Genetic Investigation of Anthropometric traits (GIANT) Consortium, which included Metabochip and GWA studies on 70,692 women aged less than 50 years (25, 26). Here BMI was based on either measured or self-reported height and weight (26), and the analyses were adjusted for age and age^2 (25). Due to the use of a rank-based inverse normal transformation of BMI in the original analyses, we could not obtain an interpretable MR estimate using these summary data, since back transformation to values in kg/m^2 is not possible without access to the individual-level data. For this reason, although we performed a similar MR analysis to the one performed with UK Biobank data, we only report results in terms of direction of the causal effect and statistical significance.

All genetic association analyses assume an additive genetic model, as well as no interactions for both SNP-age at menarche and SNP-adult BMI associations.

Mendelian randomization estimates

The MR effect estimates for each instrument were derived using the Wald estimator (27), which is the ratio of the SNP-BMI estimate over the SNP-age at menarche estimate, with the Delta method used to estimate the standard error (28). A fixed-effect inverse-variance weighted meta-analysis (IVW) was then used to combine individual MR estimates across SNPs and generate an overall estimate of the effect of age at menarche on adult BMI.

Investigation of pleiotropy

The MR analysis is based on the assumption of no horizontal pleiotropy, that is each SNP exerts its effect on adult BMI through variations in the timing of menarche, and not by any other independent pathway (29). Violation of this assumption can be assessed by evaluating, as a proxy, the variability in MR estimates across different SNPs beyond what can be expected by chance alone, using the I^2 statistic (called here I^2_{MR}) and Cochran's Q test (30). In this analysis, an I^2_{MR} value of greater than 25% or a Cochran's Q test $p<0.05$ was used to identify the presence of horizontal pleiotropy. If detected, further robust sensitivity analysis methods, which operate under weaker assumptions, were performed.

MR-Egger regression is one such method (31). It performs a linear regression of the SNP-outcome association estimates on the SNP-exposure association estimates. If the assumptions of the model are met, the intercept of this regression represents an estimate for the directional bias due to horizontal pleiotropy. An intercept estimate close to zero suggests that either there is no horizontal pleiotropy, or that the horizontal pleiotropy between different SNPs is balanced and thus effectively "cancels out". In the latter case, a random-effect IVW meta-analysis is then sufficient to address the observed pleiotropy (19), which is generally far more efficient than MR-Egger (20).

MR-Egger, fixed-effect IVW meta-analysis and random-effect IVW meta-analysis all rely on the assumption that the effect of the instruments on age at menarche is independent of any possible horizontal pleiotropic effects that they may exert, the Instrument Strength Independent of Direct Effect (InSIDE) assumption (31), although MR-Egger is much more sensitive to violations of InSIDE (20). In our scenario, a potential pleiotropic mechanism is through childhood BMI, and it might be that SNPs associated with age at menarche have a proportionate association with childhood BMI, which would violate the InSIDE assumption. For this reason, if there was an I^2_{MR} value of greater than 25% or a Cochran's Q test p<0.05 following the initial fixed-effect IVW meta-analysis of all 122 age at menarche instruments, sensitivity analysis using weighted regression-based multivariable MR was also performed, to adjust for the effects of the age at menarche instruments on childhood BMI when estimating their effect on adult BMI (32, 33). Furthermore, those SNPs also associated with childhood BMI were consequently excluded from MR analyses. SNP-childhood BMI association estimates for each of the 122 age at menarche instruments were contributed by the Early Growth Genetics (EGG) Consortium from a GWA meta-analysis that used age- and sex-adjusted standard deviation scores (34). We considered SNPs associated with childhood BMI using a p-value threshold of 4×10^{-4}, after accounting for multiple testing (Bonferroni correction for the 122 SNPs).

Two further sensitivity analyses that do not rely on the InSIDE assumption were also performed. First, the weighted median estimator calculates the mid-point of the distribution of MR estimates, while considering their relative precision, and is consistent when more than 50% of the information for the analysis comes from valid instruments (35). Second, a weighted mode-based estimator is robust when the largest number of similar causal effect estimates from individual instruments are valid, even in scenarios where most instruments are not (36).

Bias due to winner's curse

SNP-age at menarche estimates that are generated from discovery rather than replication analysis (which had a sample size 20 times smaller, 8,689 versus 182,416) (21), may result in upward bias in these estimates ("winner's curse") (37). This would lead to underestimation of the true causal effect of age at menarche on adult BMI, which in our two-sample MR study is estimated using the Wald estimator, i.e. the ratio of the SNP-adult BMI association over the SNP-age at menarche association. An unweighted allele score analysis, which is not affected by bias resulting from winner's curse, can be used to address this (38). As a further sensitivity analysis, we therefore performed a fixed-effect meta-analysis of SNP-adult BMI association estimates across instruments, which is equivalent to performing an unweighted allele score analysis with all SNPs.

All analyses were performed using Stata 14 (StataCorp LP). The weighted median estimator and the weighted mode-based estimator (with a turning parameter of 1) were performed using the mrrobust package (39).

Results

All 122 instruments demonstrated a strong association with age at menarche, with F statistics ranging from 25 to 576 (Supplementary Table 1). They all exceed the recommended threshold of 10 for MR analyses and provide assurance that the results are probably not affected by weak instrument bias (22, 23). The individual effect estimates of each instrument on age of menarche and adult BMI (UK

Biobank data) are detailed in Supplementary Tables 1 and 2 respectively. Supplementary Table 3 shows the causal effect estimate of age of menarche on adult BMI for each instrument, using SNP-adult BMI association estimates from the UK Biobank.

The main MR analyses were performed using SNP-adult BMI association estimates from the UK Biobank data. The fixed-effect IVW meta-analysis using all 122 instruments demonstrated a causal effect of age at menarche on adult BMI, with a one year increase in age at menarche causing a reduction in adult BMI of 0.56kg/m² (95% CI 0.44 to 0.68kg/m², p value = 7×10^{-19}). There was strong evidence of heterogeneity suggesting the presence of horizontal pleiotropy, with an I^2_{MR} statistic of 70% (95% CI 64% to 75%) and a Cochran's Q test p value of 3×10^{-31}. Sensitivity analysis using weighted regression-based multivariable MR that adjusted for the effects of the age at menarche instruments on childhood BMI (Supplementary Table 4) supported a smaller effect of a one year increase in age at menarche causing a reduction in adult BMI of 0.26kg/m^2 (95%CI 0.13 to 0.39kg/m^2, p value = 1×10^{-4}), and also suggested that childhood BMI was exerting horizontal pleiotropy (p = 3×10^{-65}). For this reason, the 12 age at menarche instruments also associated with childhood BMI (p < 4×10^{-4}, Supplementary Table 4) were consequently excluded from further sensitivity analyses.

The fixed-effect IVW meta-analysis using the remaining 110 instruments also demonstrated a causal effect of age at menarche on adult BMI, with a one year increase in age at menarche causing a reduction in adult BMI of 0.38kg/m² (95% CI 0.25 to 0.51kg/m², p value = 6×10^{-9}). There remained moderate evidence of heterogeneity to suggest the presence of horizontal pleiotropy, with an I^2_{MR} statistic of 46% (95% CI 33% to 57%) and a Cochran's Q test p value of 1×10^{-7}. MR-Egger regression analysis using these 110 instruments did not produce evidence of directional horizontal pleiotropy (intercept estimate -0.001, 95% CI -0.018 to 0.015, p value = 0.878), and identified a similar causal effect of age at menarche on adult BMI of 0.38kg/m² (95% CI 0.001 to 0.75, p value = 0.049). A random-effect IVW meta-analysis was performed as a sensitivity analysis in the context of possible balanced pleiotropy, and gave a similar causal effect estimate (0.40kg/m^2, 95%CI 0.21 to 0.58kg/m^2, p value = 2×10^{-5}). Sensitivity analysis using the weighted median and weighted mode-based estimator methods also demonstrated similar causal effects, with a one year increase in age at menarche causing a reduction in adult BMI of 0.41kg/m² (95%CI 0.19 to 0.63kg/m^2, p value = 3×10^{-4}) and 0.41kg/m^2 (95%CI 0.11 to 0.71kg/m^2, p = 0.007), respectively.

An unweighted allele score for the 110 age at menarche instruments (after excluding the 12 pleiotropic instruments also associated with childhood BMI) using the UK Biobank data showed an association with adult BMI (p value = 2×10^{-9}). This highlights that the causal effect of age at menarche on adult BMI identified in our main MR analysis is unlikely to be attributable to "winner's curse" bias due to the use of SNP-age at menarche estimates from discovery stage results, as the unweighted allele score does not use these estimates. Results from all the analyses performed in UK Biobank are presented in Table 1.

The fixed-effect IVW meta-analysis of MR estimates across all 122 instruments using data from the GIANT consortium confirmed an effect of age at menarche on adult BMI (p value = 3×10^{-22}), with direction consistent with that found in UK Biobank; it also showed strong evidence of heterogeneity (I^2_{MR} statistic of 72%, Cochran's Q test p value = 5×10^{-36}). When repeating the analysis after excluding the 12 SNPs associated with childhood BMI, the p value was 1×10^{-9}, with moderate evidence of heterogeneity (I^2_{MR} statistic of 43%, Cochran's Q test p value = 2×10^{-6}).

Discussion

In this study, we performed an MR analysis using UK Biobank to estimate the causal effect of age of menarche on adult BMI. There was evidence horizontal pleiotropy, and multivariable MR that accounted for the effects of the instruments on childhood BMI supported a causal effect of age at menarche on adult BMI, whilst also providing evidence that childhood BMI was contributing to the pleiotropy. After excluding the 12 age at menarche instruments also associated with childhood BMI, fixed-effect IVW meta-analysis using the remaining 110 instruments demonstrated that a one year increase in age at menarche caused a reduction in adult BMI of 0.38kg/m². However, there remained moderate evidence of horizontal pleiotropy, which may be introducing bias into this MR analysis (30). MR-Egger regression analysis did not produce any evidence of directional pleiotropy (20, 40), and sensitivity analysis with random-effect IVW meta-analysis, which can address balanced horizontal pleiotropy (19), also provided a similar estimate to the fixed-effect model. Furthermore, MR-Egger regression, the weighted median estimator and the weighted mode-based estimator all also produced a causal estimate in keeping with both IVW meta-analysis methods and multivariable MR, to further strengthen the evidence. Our findings for presence and direction of a causal effect of age at menarche in UK Biobank, which includes women aged 40 to 69 years, could be replicated using publicly available data from the GIANT Consortium on women aged less than 50 years.

Our findings support those of previous observational studies, which have shown a similar inverse relationship between the onset of menarche and adult obesity (3). Of particular note is the Framingham Heart Study (41), which investigated the association of age at menarche with BMI and adiposity in a sample of 1,456 women over the age of 40. The researchers adjusted the analyses for lifestyle factors and exogenous hormone exposure, although they note causal interpretation was limited because it was not also possible to adjust for childhood adiposity due to lack of data. Other studies, including the Bogalusa Heart Study (10), and the 1950's Aberdeen Cohort (8), were able to adjust the analyses for childhood BMI using longitudinal data, although their estimates of the impact of this confounding effect differed markedly (60-75% and 11% attenuation of the association of interest, respectively). Furthermore, whilst these studies adjusted for various other confounding factors, it is likely that some unknown confounders may remain. In addition, the authors of both papers note that selection bias due to loss of follow up or missing data may have impacted on the results. In this study, we used genetic variants as instruments in an MR analysis to overcome these limitations of observational research. While recent work has already demonstrated a strong inverse genetic correlation between age at menarche and adult BMI, with MR used to highlight the causal effect of age at menarche on adult BMI (17), our current study goes further beyond this to estimate the magnitude of this effect, and also uses a number of sensitivity analyses to show that it is robust to the presence of horizontal pleiotropy.

Explanations for the detrimental health outcomes in adulthood attributable to earlier age at puberty span a range of domains (42). Early menarche hastens exposure to gonadal steroids, invoking accelerated physical and psychological changes. Oestrogen and progesterone receptors are widely expressed in adipose tissue, and are thought to mediate variations in body habitus patterns between genders (43). Pre-pubertal girls with greater abdominal fat have been shown to have increased plasma levels of total oestradiol compared to their leaner peers (44). Interestingly, these girls also had an

accelerated progression through pubertal stages, implicating gonadal steroids as mediators of the faster maturation seen with earlier menarche (45). However observational studies of women using oestrogen-based hormonal contraceptives have failed to identify any dose-related effect on weight gain, suggesting that adiposity changes are unlikely to be solely oestrogen-dependant (46). Hyperandrogenemia (excessively high androgen concentrations) may also play a role in mediating increased adult BMI (47), although the contribution of individual androgens remains to be established. A cross-sectional study by Bleil and colleagues found that the association between pubertal timing and adult obesity was attenuated after accounting for biologically active testosterone levels (48). In contrast, a more recent study by Gallachio and colleagues found relatively little attenuation after this adjustment, although they note that other androgens such as dehydroepiandrosterone-sulfate (DHEA-S) may have a role (49). Supporting the androgen hypothesis, evidence from studies on precocious puberty show that early adrenarche (maturational increase in adrenal androgen production) is associated with ovarian hyperandrogenism (50). The cause of the hyperandrogenaemia is unclear, however it may in part be due to positive feedback regulation on gonadotrophin release in the hypothalamus from elevated oestrogen levels (51). The roles of androgens in insulin resistance and obesity have also been well-described (52).

The effects of an altered hormonal environment may also impact on the psychological development of adolescent girls, which may in turn increase susceptibility for weight gain (42). Enduring the accelerated physical changes of puberty discordantly with peers can predispose to negative effects in early adolescence (45). Of particular interest is the association with depressive disorders, which have a complex bi-directional relationship with obesity (53). A meta-analysis by Blaine et al found that female adolescent depression increased the risk of adult obesity by more than two-fold (54). Proposed explanations for this effect include emotional eating behaviours, less time spent engaging in physical activity, and changes in adiposity secondary to antidepressant use. Weight gain at this age is stigmatizing, reinforcing discrimination and social isolation from others (55). This in turn may exacerbate depression and precipitate adult obesity. Early maturing girls have also been shown to achieve poorer academic and employment outcomes in relation to their peers (56). This has been partly attributed to accelerated involvement in romantic relationships and truant behaviour, distracting girls from academic work and leading to school absenteeism (42). Schooling provides consistently timetabled physical activity, as well as encouraging children to take part in sports outside of lesson time. Whilst the efficacy of school programmes on limiting obesity remain controversial, overall estimates show a beneficial effect (57).

Schulz et al. provide another theory bridging these models that attributes the psychological outcomes to varying gonadal steroid exposure during early adolescence (58). They propose that hormonal organising events on the brain are chronologically influenced, due to declining neural plasticity following the postnatal period. Girls who undergo earlier menarche may develop emotional responses discordantly with the cognitive control systems that are achieved later in adolescence (59, 60). This may predispose them to negative interpretation of environmental and social events, giving rise to detrimental psychological outcomes that persist into adult life. It is indeed likely that the psychological and biological consequences of early puberty synergise to create an at-risk phenotype for excessive weight gain. The propensity to follow this path may be dictated by the environmental and social context.

316 The effects of common genetic variants are typically modest and this was the case with age at
317 menarche in our current MR study, where adequate instrument strength could only be achieved
318 because of the large sample size of the GWA study. For this reason, we used SNP-age at menarche
319 estimates generated from the discovery (rather than the replication) analysis, but these might be
320 affected by the upward bias typical of the discovery stage (winner's curse bias) (37), resulting in
321 overestimation of the SNP-age at menarche association to pull the MR estimate towards the null and
322 give a false positive result. Reassuringly however, our sensitivity analysis suggested that the identified
323 causal effect of age at menarche and adult BMI is not attributable to such possible bias.

324 In conclusion, this study demonstrates a causal effect of age at menarche on adult BMI. This supports
325 previous research and helps provide further mechanistic insight into the influence pubertal timing has
326 on adult obesity. We propose elevated gonadal hormones and adverse psychological outcomes as
327 possible mediators for the observed effect.

Conflict of Interest

All authors declare no conflict of interest. Specially, no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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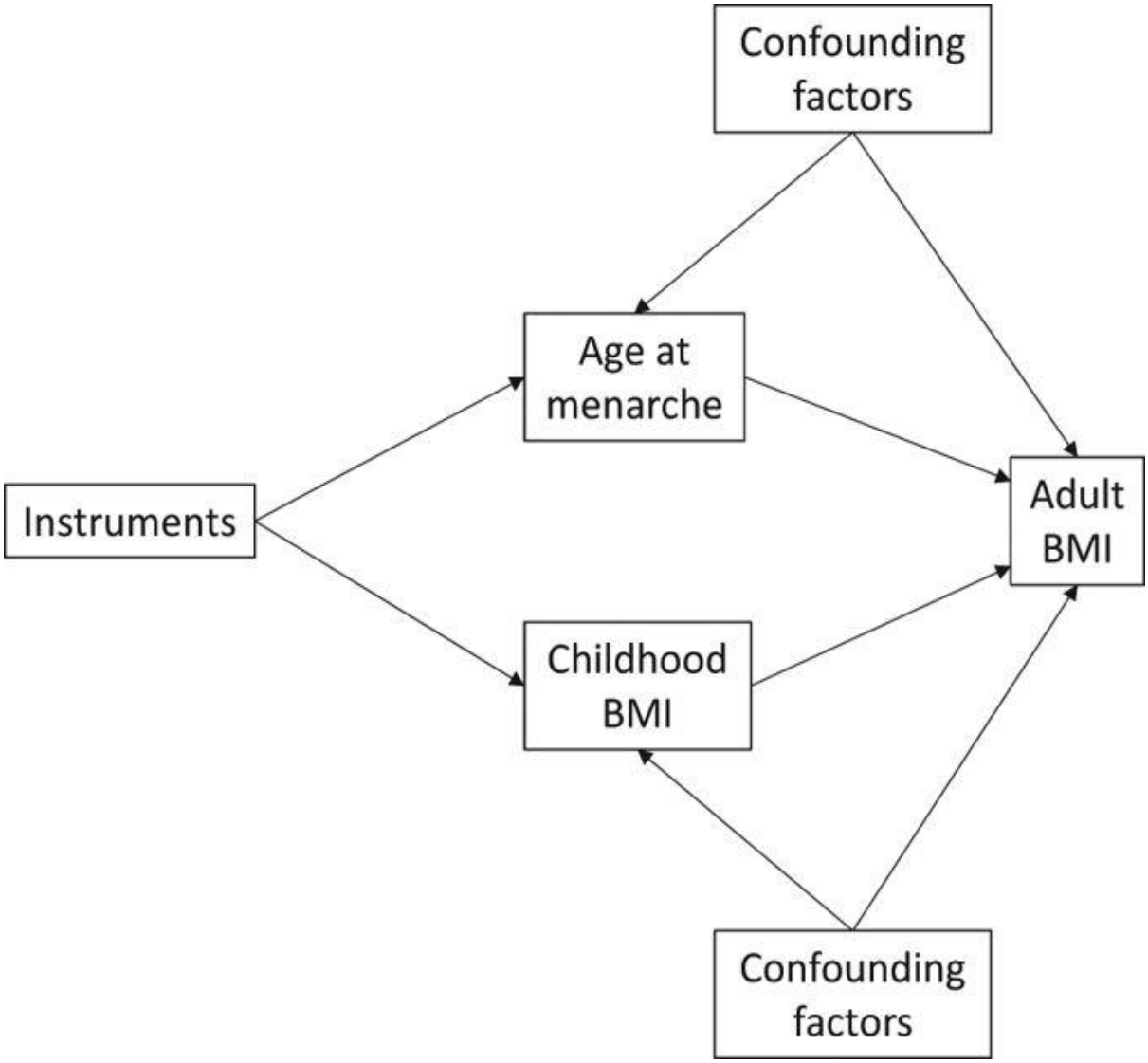
Figure legend

A directed acyclic graph depicting the application of multivariable Mendelian randomization in this context. The instruments for age at menarche may also have a causal effect on childhood BMI and thus affect adult BMI through this pathway. The multivariable Mendelian randomization approach allows adjustment for the effects of the age at menarche instruments on childhood BMI when estimating their effect on adult BMI. An assumption in this model is that all instruments affect adult BMI only through age at menarche or childhood BMI and no other pathway



493 # Table Legend

494 **Table 1**. MR estimates of the causal effect from the analyses performed in UK Biobank.

SNPs	Mendelian randomization analysis	MR estimate kg/m^2 (95% CI)	*p*-Value
All 122	Fixed-effect IVW meta-analysis	0.56 (0.44–0.68)	7×10^{-19}
	Weighted regression-based multivariable MR (adjusted for childhood BMI)	0.26 (0.13–0.39)	1×10^{-4}
110 (excluding the 12 SNPs also associated with childhood BMI)	Fixed-effect IVW meta-analysis	0.38 (0.25–0.51)	6×10^{-9}
	MR-Egger slope (causal effect)	0.38 (0.001–0.75)	0.049
	Random-effect IVW meta-analysis	0.40 (0.21–0.58)	2×10^{-5}
	Weighted median estimator	0.41 (0.19–0.63)	3×10^{-4}
	Weighted mode-based estimator	0.41 (0.11–0.71)	0.007

495

Supplementary Table Legends

Supplementary Table 1. Estimates of the SNP-age at menarche association for all 122 SNPs, from Perry et al. (1). EA: effect allele; EAF: effect allele frequency; F: F statistic, a function of the magnitude and precision of the genetic effect estimated as: $F=GX^2/GX\ SE^2$ (2); GX: per-allele genetic effect on age at menarche (years); GX SE: standard error of GX; p: p value of GX

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SNP	Gene	EA	EAF	F	GX	GX SE	p
rs10144321	*DLK1*	a	0.75	44	0.04	0.006	9.0E-15
rs1038903	*PCDH7*	t	0.73	44	0.04	0.006	2.0E-11
rs10423674	*CRTC1*	a	0.34	64	0.04	0.005	9.2E-12
rs10453225	*TMEM38B*	g	0.68	324	0.09	0.005	5.8E-66
rs10739221	*TMEM38B*	c	0.77	178	0.08	0.006	3.9E-41
rs10789181	*LEPR*	a	0.39	36	0.03	0.005	3.5E-08
rs1079866	*INHBA*	g	0.15	100	0.07	0.007	9.3E-24
rs10816359	*TMEM38B*	t	0.86	25	0.04	0.008	1.6E-08
rs10895140	*TRPC6, PGR*	g	0.66	64	0.04	0.005	6.7E-14
rs10938397	*GNPDA2*	a	0.57	64	0.04	0.005	4.0E-13
rs10980854	*ZNF483 / OR2K2*	a	0.06	30	0.06	0.011	1.3E-08
rs10980921	*ZNF483 / OR2K2*	c	0.09	100	0.09	0.009	1.7E-23
rs11022756	*ARNTL, PTH*	a	0.29	69	0.05	0.006	7.4E-20
rs11165924	*DPYD*	a	0.69	25	0.03	0.006	2.2E-09
rs11215400	*CADM1*	c	0.27	44	0.04	0.006	6.8E-11
rs1129700	*KCTD13, TBX6*	t	0.44	36	0.03	0.005	2.3E-09
rs11578152	*OLFM3*	g	0.44	36	0.03	0.005	4.5E-08

rs11715566	*IGSF11*	t	0.5	100	0.05	0.005	2.4E-27
rs11767400	*CADPS2*	a	0.3	44	0.04	0.006	4.1E-11
rs11792861	*TMEM245*	a	0.7	64	0.04	0.005	1.7E-11
rs12148769	*MKRN3, MAGEL2*	g	0.9	39	0.05	0.008	5.2E-11
rs12446632	*GPRC5B*	a	0.13	33	0.04	0.007	1.3E-08
rs12472911	*LRP1B*	c	0.2	44	0.04	0.006	6.7E-10
rs1254337	*SIX6*	t	0.31	64	0.04	0.005	2.1E-16
rs12571664	*SEC23IP*	t	0.79	44	0.04	0.006	3.3E-10
rs12607903	*DLGAP1*	c	0.3	64	0.04	0.005	5.4E-11
rs12915845	*DET1*	c	0.58	36	0.03	0.005	2.7E-12
rs13053505	*NPTXR, CBX7*	g	0.8	33	0.04	0.007	3.0E-08
rs13067731	*IL20RB*	t	0.16	33	0.04	0.007	1.0E-09
rs13135934	*SMARCAD1*	c	0.4	36	0.03	0.005	1.1E-10
rs13179411	*PHF15, TCF7*	t	0.17	73	0.06	0.007	3.4E-20
rs13196561	*SIM1, MCHR2*	c	0.78	44	0.04	0.006	8.4E-12
rs1324913	*KLF12*	g	0.65	36	0.03	0.005	3.1E-10
rs1364063	*COG4, NFAT5*	c	0.43	100	0.05	0.005	6.2E-21
rs1400974	*SATB2*	a	0.64	100	0.05	0.005	8.3E-20
rs1461503	*BSX*	c	0.57	100	0.05	0.005	2.7E-26
rs1469039	*KCNK9*	a	0.19	51	0.05	0.007	3.5E-12
rs1532331	*ZNF131, GHR*	g	0.32	36	0.03	0.005	3.5E-09
rs16860328	*TRA2B, IGF2BP2*	g	0.42	64	0.04	0.005	1.4E-16
rs16896742	*HLA-A*	g	0.38	44	0.04	0.006	3.2E-10
rs16918254	*NPBWR1*	a	0.92	31	0.05	0.009	1.4E-08
rs16918636	*FSHB*	t	0.79	25	0.03	0.006	3.2E-08

rs17086188	*PCSK1*	a	0.94	29	0.07	0.013	3.6E-08
rs17171818	*KDM3B, BRD8*	c	0.77	44	0.04	0.006	8.9E-14
rs17233066	*SATB2*	c	0.93	41	0.09	0.014	6.1E-11
rs17236969	*NR4A2*	t	0.14	39	0.05	0.008	2.6E-09
rs17266097	*SATB2*	t	0.42	64	0.04	0.005	3.3E-18
rs1874984	*ADARB2*	c	0.47	64	0.04	0.005	1.9E-12
rs1915146	*CTBP2*	g	0.4	36	0.03	0.005	3.7E-08
rs1958560	*FUT8*	a	0.59	36	0.03	0.005	3.7E-08
rs2063730	*GAB2, THRSP*	c	0.18	51	0.05	0.007	2.3E-12
rs2137289	*SKOR2*	a	0.59	100	0.05	0.005	8.2E-20
rs2153127	*LIN28B*	t	0.52	256	0.08	0.005	5.5E-59
rs2274465	*KDM4A, PTPRF*	c	0.66	36	0.03	0.005	1.7E-09
rs239198	*SIM1, ASCC3*	t	0.46	36	0.03	0.005	2.5E-08
rs244293	*STXBP4*	g	0.6	36	0.03	0.005	4.2E-11
rs246185	*MKL2*	c	0.33	44	0.04	0.006	6.8E-16
rs2479724	*BYSL, FRS3*	t	0.45	36	0.03	0.005	1.2E-12
rs251130	*STARD4*	g	0.73	44	0.04	0.006	2.8E-10
rs2600959	*ACAD11*	a	0.34	64	0.04	0.005	4.1E-11
rs268067	*BCL11A*	a	0.8	44	0.04	0.006	3.3E-08
rs2687729	*EEFSEC*	g	0.27	44	0.04	0.006	1.0E-10
rs2688325	*CSMD1*	t	0.29	25	0.03	0.006	2.1E-09
rs2836950	*BRWD1*	c	0.64	36	0.03	0.005	6.2E-11
rs2947411	*TMEM18*	a	0.17	73	0.06	0.007	1.8E-19
rs3101336	*NEGR1*	t	0.4	64	0.04	0.005	5.2E-13
rs3733631	*TACR3*	c	0.15	51	0.05	0.007	4.8E-13

rs3743266	*RORA*	t	0.68	64	0.04	0.005	2.4E-13
rs4369815	*NR4A2*	t	0.93	36	0.06	0.01	1.5E-10
rs466639	*RXRG*	c	0.87	131	0.08	0.007	2.4E-24
rs4756059	*PHF21A*	t	0.92	49	0.07	0.01	4.5E-13
rs4840086	*SIM1, MCHR2*	a	0.58	64	0.04	0.005	9.2E-14
rs4875053	*SCRIB, PARP10*	g	0.44	25	0.03	0.006	1.3E-08
rs4895808	*CENPW, NCOA7*	c	0.54	36	0.03	0.005	4.8E-13
rs4929947	*TRIM66*	g	0.36	64	0.04	0.005	2.6E-12
rs543874	*SEC16B*	a	0.8	69	0.05	0.006	1.4E-15
rs6009583	*C22orf34*	c	0.74	25	0.03	0.006	4.6E-08
rs6427782	*NR5A2*	a	0.51	36	0.03	0.005	4.6E-08
rs652260	*EVI5L, RETN*	t	0.54	36	0.03	0.005	9.9E-09
rs6555855	*SLIT3*	g	0.23	44	0.04	0.006	2.4E-09
rs6563739	*COG6*	g	0.34	36	0.03	0.005	2.3E-11
rs6747380	*CCDC85A*	a	0.17	100	0.07	0.007	5.6E-28
rs6758290	*GPR45*	t	0.5	64	0.04	0.005	6.6E-13
rs6762477	*WDR6, UBA7*	g	0.44	44	0.04	0.006	7.8E-12
rs6770162	*THRB*	a	0.51	64	0.04	0.005	1.5E-12
rs6933660	*ESR1*	c	0.69	36	0.03	0.005	1.3E-09
rs6938574	*PTPRK*	t	0.16	33	0.04	0.007	2.4E-09
rs6964833	*GTF2I*	t	0.75	44	0.04	0.006	5.3E-12
rs7037266	*KDM4C*	a	0.37	36	0.03	0.005	4.7E-09
rs7103411	*BDNF, LGR4*	c	0.21	44	0.04	0.006	2.6E-11
rs7104764	*SIRT3*	g	0.25	25	0.03	0.006	3.7E-08
rs7138803	*BCDIN3D*	g	0.62	64	0.04	0.005	1.7E-12

rs7141210	*DLK1*	t	0.34	36	0.03	0.005	5.8E-09
rs7215990	*WSCD1 , ALOX15B*	g	0.76	44	0.04	0.006	1.9E-08
rs7463166	*CSMD1*	a	0.63	36	0.03	0.005	1.3E-08
rs7514705	*TNNI3K, TYW3*	c	0.56	64	0.04	0.005	1.8E-16
rs7642134	*POU1F1 (PIT1)*	g	0.61	64	0.04	0.005	3.0E-16
rs7647973	*WDR6, UBA7*	a	0.26	69	0.05	0.006	1.3E-16
rs7701886	*GALNT10*	a	0.58	36	0.03	0.005	4.5E-08
rs7759938	*LIN28B*	c	0.32	576	0.12	0.005	7.8E-110
rs7821178	*PEX2*	c	0.65	64	0.04	0.005	7.3E-17
rs7828501	*CSMD1*	g	0.45	64	0.04	0.005	1.2E-13
rs7853970	*RMI1, NTRK2*	t	0.47	36	0.03	0.005	2.3E-09
rs7865468	*PTPRD*	a	0.7	36	0.03	0.005	1.3E-07
rs7955374	*VDR*	t	0.13	25	0.04	0.008	9.5E-09
rs8032675	*MAP2K5*	t	0.4	64	0.04	0.005	2.1E-13
rs8050136	*FTO*	c	0.6	64	0.04	0.005	1.7E-17
rs852069	*PCSK2*	g	0.64	64	0.04	0.005	1.2E-13
rs889122	*OLFM2, RDH8*	g	0.72	44	0.04	0.006	1.6E-13
rs900400	*LEKR1, CCNL1*	t	0.61	36	0.03	0.005	2.3E-11
rs913588	*KDM4C*	g	0.49	36	0.03	0.005	5.8E-11
rs929843	*COG4, WWP2*	a	0.23	44	0.04	0.006	1.2E-11
rs9321659	*SIM1, MCHR2*	a	0.13	56	0.06	0.008	2.5E-16
rs939317	*EIF4G1*	g	0.74	44	0.04	0.006	3.0E-12
rs9447700	*IMPG1*	c	0.69	36	0.03	0.005	5.6E-09
rs9475752	*DST, BEND6*	c	0.81	44	0.04	0.006	8.3E-12
rs951366	*NUCKS1, RAB7L1*	t	0.6	36	0.03	0.005	1.7E-08

rs9560113	*TEX29*	g	0.28	69	0.05	0.006	2.1E-17
rs9635759	*CA10*	a	0.32	100	0.05	0.005	1.7E-24
rs9647570	*TENM2*	g	0.14	51	0.05	0.007	1.4E-11
rs9849248	*ZNF654, HTR1F*	c	0.15	33	0.04	0.007	1.9E-08
rs988913	*FAM83B, HCRTR2*	c	0.66	64	0.04	0.005	1.4E-12

501

502 **Supplementary Table 2**. Estimates of the SNP-adult BMI association for all 122 SNPs, from the UK
503 Biobank (3). EA: effect allele; GY: per-allele genetic effect on adult BMI (kg/m²); GY SE: standard error
504 of GY; p: p value of GY

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SNP	EA	GY	GY SE	p
rs10144321	a	0.0108	0.0316	0.7446
rs1038903	t	0.0304	0.0282	0.2845
rs10423674	a	-0.1019	0.0277	0.0003
rs10453225	g	-0.0082	0.0283	0.7857
rs10739221	c	-0.0228	0.0311	0.4726
rs10789181	a	-0.0654	0.0268	0.0147
rs1079866	g	0.0513	0.0382	0.1802
rs10816359	t	-0.0794	0.0360	0.0271
rs10895140	g	0.0041	0.0272	0.8900

rs10938397	a	-0.1704	0.0263	3.E-10
rs10980854	a	-0.0591	0.0566	0.3002
rs10980921	c	-0.1046	0.0469	0.0255
rs11022756	a	-0.0459	0.0272	0.0906
rs11165924	a	-0.0090	0.0281	0.7606
rs11215400	c	-0.0297	0.0300	0.3268
rs1129700	t	-0.0944	0.0262	0.0003
rs11578152	g	-0.0038	0.0262	0.8945
rs11715566	t	-0.0502	0.0259	0.0524
rs11767400	a	0.0356	0.0289	0.2200
rs11792861	a	0.0008	0.0290	0.9811
rs12148769	g	-0.0805	0.0438	0.0654
rs12446632	a	-0.1863	0.0374	9.E-07
rs12472911	c	-0.0319	0.0305	0.3000
rs1254337	t	0.0646	0.0285	0.0231
rs12571664	t	-0.0341	0.0348	0.3310
rs12607903	c	-0.0172	0.0272	0.5366

rs12915845	c	-0.0093	0.0264	0.7386
rs13053505	g	-0.0293	0.0368	0.4347
rs13067731	t	0.0039	0.0354	0.9191
rs13135934	c	0.0086	0.0266	0.7600
rs13179411	t	-0.0890	0.0378	0.0183
rs13196561	c	-0.0275	0.0332	0.4148
rs1324913	g	0.0279	0.0278	0.3196
rs1364063	c	-0.1292	0.0266	2.E-06
rs1400974	a	0.0144	0.0243	0.5667
rs1461503	c	-0.0121	0.0259	0.6515
rs1469039	a	-0.0362	0.0373	0.3373
rs1532331	g	-0.0092	0.0253	0.7297
rs16860328	g	-0.0262	0.0263	0.3235
rs16896742	g	-0.0367	0.0270	0.1745
rs16918254	a	0.0171	0.0509	0.7500
rs16918636	t	-0.0023	0.0324	0.9486
rs17086188	a	-0.1028	0.0805	0.2029
rs17171818	c	-0.0129	0.0320	0.7011

rs17233066	c	-0.0290	0.0532	0.5979
rs17236969	t	0.0504	0.0369	0.1730
rs17266097	t	-0.0172	0.0270	0.5336
rs1874984	c	-0.0342	0.0260	0.1896
rs1915146	g	-0.0213	0.0265	0.4295
rs1958560	a	-0.0304	0.0264	0.2524
rs2063730	c	-0.0304	0.0331	0.3637
rs2137289	a	-0.0615	0.0253	0.0150
rs2153127	t	-0.0124	0.0258	0.6445
rs2274465	c	0.0088	0.0275	0.7610
rs239198	t	-0.0345	0.0259	0.1845
rs244293	g	-0.0184	0.0249	0.4689
rs246185	c	-0.0390	0.0288	0.1769
rs2479724	t	0.0105	0.0260	0.6998
rs251130	g	-0.0241	0.0294	0.4200
rs2600959	a	0.0145	0.0257	0.5843
rs268067	a	-0.0389	0.0308	0.2090
rs2687729	g	-0.0233	0.0294	0.4369

rs2688325	t	0.0122	0.0250	0.6380
rs2836950	c	-0.0576	0.0272	0.0338
rs2947411	a	-0.2740	0.0342	8.E-15
rs3101336	t	-0.1335	0.0266	8.E-07
rs3733631	c	-0.0370	0.0361	0.3090
rs3743266	t	0.0071	0.0277	0.8107
rs4369815	t	-0.0245	0.0540	0.6630
rs466639	c	-0.0482	0.0393	0.2221
rs4756059	t	0.0839	0.0423	0.0467
rs4840086	a	-0.0318	0.0264	0.2301
rs4875053	g	-0.0351	0.0263	0.1821
rs4895808	c	0.0480	0.0262	0.0667
rs4929947	g	-0.1436	0.0270	2.E-07
rs543874	a	-0.3220	0.0321	4.E-22
rs6009583	c	0.0456	0.0304	0.1334
rs6427782	a	0.0184	0.0261	0.4914
rs652260	t	0.0257	0.0256	0.3205
rs6555855	g	-0.0354	0.0322	0.2745
rs6563739	g	0.0556	0.0275	0.0425

rs6747380	a	0.0583	0.0350	0.0957
rs6758290	t	-0.0230	0.0258	0.3790
rs6762477	g	0.0937	0.0262	0.0004
rs6770162	a	-0.0388	0.0253	0.1258
rs6933660	c	-0.0097	0.0281	0.7442
rs6938574	t	-0.0172	0.0317	0.5984
rs6964833	t	-0.0694	0.0301	0.0209
rs7037266	a	-0.0737	0.0271	0.0066
rs7103411	c	-0.1574	0.0320	1.E-06
rs7104764	g	-0.0534	0.0287	0.0630
rs7138803	g	-0.1572	0.0270	1.E-08
rs7141210	t	0.0204	0.0278	0.4723
rs7215990	g	-0.0556	0.0326	0.0879
rs7463166	a	0.0273	0.0272	0.3218
rs7514705	c	-0.1048	0.0265	0.0001
rs7642134	g	0.0300	0.0268	0.2651
rs7647973	a	0.0376	0.0301	0.2140
rs7701886	a	-0.0841	0.0256	0.0010

rs7759938	c	-0.0498	0.0278	0.0731
rs7821178	c	-0.0160	0.0283	0.5832
rs7828501	g	0.0025	0.0260	0.9292
rs7853970	t	0.0111	0.0250	0.6691
rs7865468	a	0.0181	0.0242	0.4641
rs7955374	t	0.0330	0.0431	0.4522
rs8032675	t	-0.0924	0.0249	0.0002
rs8050136	c	-0.3674	0.0266	1.E-39
rs852069	g	-0.0565	0.0270	0.0363
rs889122	g	-0.0360	0.0292	0.2197
rs900400	t	-0.0105	0.0285	0.7243
rs913588	g	-0.0193	0.0261	0.4694
rs929843	a	-0.0708	0.0310	0.0220
rs9321659	a	-0.0132	0.0390	0.7490
rs939317	g	-0.0664	0.0274	0.0153
rs9447700	c	0.0098	0.0282	0.7418
rs9475752	c	0.0376	0.0329	0.2569
rs951366	t	0.0378	0.0250	0.1306
rs9560113	g	-0.0289	0.0293	0.3282

rs9635759	a	-0.0122	0.0284	0.6801
rs9647570	g	-0.0628	0.0383	0.1011
rs9849248	c	-0.0629	0.0348	0.0705
rs988913	c	0.0314	0.0276	0.2586

505

506 **Supplementary Table 3**. MR estimates of the causal effect of age at menarche on adult BMI for all 122
507 SNPs. EA: effect allele; Beta: estimate of the effect of one year increase in age at menarche on BMI
508 (kg/m²); Beta SE: standard error of beta; p: p value of Beta

SNP	EA	Beta	Beta SE	p
rs10144321	a	0.271	0.790	0.745
rs1038903	t	0.760	0.715	0.292
rs10423674	a	-2.546	0.762	0.001
rs10453225	g	-0.091	0.315	0.785
rs10739221	c	-0.285	0.390	0.474
rs10789181	a	-2.180	0.966	0.024
rs1079866	g	0.732	0.550	0.184
rs10816359	t	-1.986	0.984	0.043
rs10895140	g	0.102	0.679	0.89
rs10938397	a	-4.260	0.846	7E-07
rs10980854	a	-0.986	0.961	0.309
rs10980921	c	-1.162	0.534	0.029
rs11022756	a	-0.918	0.554	0.097
rs11165924	a	-0.301	0.939	0.761
rs11215400	c	-0.742	0.757	0.332
rs1129700	t	-3.147	1.018	0.002

rs11578152	g	-0.125	0.872	0.895
rs11715566	t	-1.003	0.528	0.057
rs11767400	a	0.891	0.736	0.228
rs11792861	a	0.019	0.726	0.981
rs12148769	g	-1.610	0.912	0.077
rs12446632	a	-4.657	1.241	2E-04
rs12472911	c	-0.798	0.772	0.306
rs1254337	t	1.615	0.740	0.029
rs12571664	t	-0.854	0.879	0.336
rs12607903	c	-0.431	0.681	0.538
rs12915845	c	-0.309	0.882	0.739
rs13053505	g	-0.732	0.930	0.439
rs13067731	t	0.098	0.884	0.919
rs13135934	c	0.286	0.888	0.760
rs13179411	t	-1.484	0.653	0.023
rs13196561	c	-0.688	0.837	0.419
rs1324913	g	0.930	0.938	0.326
rs1364063	c	-2.584	0.591	2E-05
rs1400974	a	0.287	0.487	0.567
rs1461503	c	-0.243	0.518	0.652
rs1469039	a	-0.724	0.754	0.342
rs1532331	g	-0.306	0.845	0.730
rs16860328	g	-0.655	0.662	0.328
rs16896742	g	-0.918	0.689	0.184
rs16918254	a	0.342	1.019	0.75

rs16918636	t	-0.076	1.080	0.949
rs17086188	a	-1.469	1.182	0.216
rs17171818	c	-0.322	0.803	0.701
rs17233066	c	-0.322	0.593	0.599
rs17236969	t	1.008	0.755	0.183
rs17266097	t	-0.431	0.677	0.535
rs1874984	c	-0.856	0.660	0.196
rs1915146	g	-0.710	0.891	0.434
rs1958560	a	-1.014	0.897	0.261
rs2063730	c	-0.608	0.666	0.368
rs2137289	a	-1.230	0.521	0.018
rs2153127	t	-0.155	0.323	0.644
rs2274465	c	0.295	0.919	0.761
rs239198	t	-1.150	0.886	0.195
rs244293	g	-0.613	0.836	0.472
rs246185	c	-0.976	0.736	0.186
rs2479724	t	0.349	0.867	0.701
rs251130	g	-0.603	0.741	0.423
rs2600959	a	0.363	0.645	0.586
rs268067	a	-0.972	0.784	0.217
rs2687729	g	-0.582	0.740	0.440
rs2688325	t	0.406	0.836	0.64
rs2836950	c	-1.919	0.960	0.045
rs2947411	a	-4.566	0.780	1E-08
rs3101336	t	-3.337	0.785	3E-05

rs3733631	c	-0.741	0.729	0.314
rs3743266	t	0.177	0.693	0.81
rs4369815	t	-0.408	0.902	0.664
rs466639	c	-0.602	0.494	0.225
rs4756059	t	1.199	0.628	0.056
rs4840086	a	-0.796	0.667	0.235
rs4875053	g	-1.172	0.907	0.198
rs4895808	c	1.600	0.913	0.079
rs4929947	g	-3.591	0.811	1E-05
rs543874	a	-6.440	1.004	4E-10
rs6009583	c	1.521	1.058	0.151
rs6427782	a	0.613	0.878	0.495
rs652260	t	0.855	0.865	0.328
rs6555855	g	-0.885	0.815	0.281
rs6563739	g	1.853	0.966	0.055
rs6747380	a	0.833	0.508	0.101
rs6758290	t	-0.575	0.648	0.382
rs6762477	g	2.343	0.744	0.002
rs6770162	a	-0.970	0.645	0.133
rs6933660	c	-0.322	0.939	0.745
rs6938574	t	-0.431	0.795	0.6
rs6964833	t	-1.736	0.796	0.029
rs7037266	a	-2.458	0.993	0.013
rs7103411	c	-3.936	0.993	9E-05
rs7104764	g	-1.778	1.022	0.082
rs7138803	g	-3.929	0.834	3E-06

rs7141210	t	0.680	0.933	0.476
rs7215990	g	-1.389	0.841	0.098
rs7463166	a	0.909	0.921	0.329
rs7514705	c	-2.621	0.739	4E-04
rs7642134	g	0.751	0.676	0.27
rs7647973	a	0.752	0.609	0.219
rs7701886	a	-2.804	0.972	0.004
rs7759938	c	-0.415	0.233	0.074
rs7821178	c	-0.400	0.709	0.584
rs7828501	g	0.063	0.651	0.929
rs7853970	t	0.371	0.835	0.670
rs7865468	a	0.603	0.814	0.468
rs7955374	t	0.826	1.090	0.457
rs8032675	t	-2.310	0.687	8E-04
rs8050136	c	-9.184	1.326	2E-11
rs852069	g	-1.412	0.698	0.043
rs889122	g	-0.900	0.742	0.227
rs900400	t	-0.351	0.951	0.725
rs913588	g	-0.642	0.876	0.473
rs929843	a	-1.771	0.819	0.03
rs9321659	a	-0.219	0.651	0.749
rs939317	g	-1.660	0.729	0.023
rs9447700	c	0.327	0.943	0.742
rs9475752	c	0.939	0.835	0.264
rs951366	t	1.259	0.859	0.143
rs9560113	g	-0.578	0.589	0.332

rs9635759	a	-0.245	0.569	0.680
rs9647570	g	-1.256	0.786	0.110
rs9849248	c	-1.572	0.913	0.085
rs988913	c	0.785	0.697	0.263

509

510 **Supplementary Table 4**. Estimates of the SNP-childhood BMI association for all 122 SNPs, from Felix
511 et al. (4). EA: effect allele; GZ: per-allele genetic effect on childhood BMI (standard deviation score);
512 GZ SE: standard error of GZ; p: p value of GZ

References

1. Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesi A, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. Hum Mol Genet. 2016;25(2):389-403.

513

SNP	EA	GZ	GZ SE	p
rs10144321	a	0.0082	0.0096	0.3915
rs1038903	t	0.0050	0.0094	0.5946
rs10423674	a	-0.0043	0.0087	0.6202
rs10453225	g	0.0016	0.0088	0.8594
rs10739221	c	-0.0096	0.0099	0.3326
rs10789181	a	0.0018	0.0087	0.8395
rs1079866	g	0.0090	0.0117	0.4377
rs10816359	t	0.0214	0.0146	0.1426
rs10895140	g	0.0065	0.0086	0.4466
rs10938397	a	-0.0497	0.0083	2E-09
rs10980854	a	-0.0331	0.0174	0.0567
rs10980921	c	-0.0208	0.0148	0.1596
rs11022756	a	-0.0017	0.0091	0.8556
rs11165924	a	-0.0017	0.0092	0.8500
rs11215400	c	-0.0361	0.0095	0.0001
rs1129700	t	-0.0201	0.0086	0.0192

rs11578152	g	-0.0038	0.0083	0.6447
rs11715566	t	-0.0089	0.0083	0.2871
rs11767400	a	0.0058	0.0091	0.5244
rs11792861	a	0.0067	0.0091	0.4601
rs12148769	g	-0.0170	0.0133	0.2014
rs12446632	a	-0.0684	0.0113	1E-09
rs12472911	c	-0.0125	0.0104	0.2324
rs1254337	t	0.0168	0.0092	0.0681
rs12571664	t	-0.0140	0.0102	0.1718
rs12607903	c	0.0021	0.0093	0.8233
rs12915845	c	-0.0004	0.0085	0.9657
rs13053505	g	-0.0030	0.0107	0.7781
rs13067731	t	0.0016	0.0114	0.8892
rs13135934	c	-0.0151	0.0093	0.1030
rs13179411	t	-0.0041	0.0112	0.7126
rs13196561	c	-0.0261	0.0101	0.0098
rs1324913	g	0.0083	0.0087	0.3435
rs1364063	c	-0.0201	0.0083	0.0156
rs1400974	a	-0.0074	0.0088	0.3995
rs1461503	c	-0.0193	0.0084	0.0209
rs1469039	a	-0.0084	0.0104	0.4184
rs1532331	g	-0.0180	0.0089	0.0426
rs16860328	g	-0.0111	0.0084	0.1874
rs16896742	g	0.0011	0.0081	0.8949
rs16918254	a	0.0252	0.0160	0.1143
rs16918636	t	-0.0070	0.0100	0.4831
rs17086188	a	-0.0272	0.0182	0.1348
rs17171818	c	-0.0074	0.0100	0.4546
rs17233066	c	0.0156	0.0234	0.5038

rs17236969	t	0.0078	0.0126	0.5378
rs17266097	t	-0.0251	0.0085	0.0033
rs1874984	c	-0.0004	0.0089	0.9614
rs1915146	g	-0.0019	0.0086	0.8199
rs1958560	a	-0.0069	0.0084	0.4075
rs2063730	c	0.0121	0.0100	0.2265
rs2137289	a	0.0006	0.0094	0.9499
rs2153127	t	-0.0181	0.0083	0.0299
rs2274465	c	0.0094	0.0087	0.2766
rs239198	t	-0.0172	0.0083	0.0382
rs244293	g	-0.0229	0.0084	0.0065
rs246185	c	-0.0025	0.0086	0.7719
rs2479724	t	-0.0032	0.0083	0.7037
rs251130	g	-0.0045	0.0092	0.6225
rs2600959	a	0.0018	0.0082	0.8278
rs268067	a	0.0094	0.0106	0.3746
rs2687729	g	-0.0258	0.0092	0.0050
rs2688325	t	0.0042	0.0085	0.6197
rs2836950	c	0.0232	0.0097	0.0168
rs2947411	a	-0.0926	0.0102	1E-19
rs3101336	t	-0.0432	0.0079	4E-08
rs3733631	c	0.0092	0.0114	0.4197
rs3743266	t	-0.0055	0.0091	0.5461
rs4369815	t	-0.0262	0.0188	0.1638
rs466639	c	0.0269	0.0124	0.0294
rs4756059	t	-0.0009	0.0151	0.9500
rs4840086	a	-0.0039	0.0084	0.6436
rs4875053	g	-0.0001	0.0092	0.9879
rs4895808	c	0.0015	0.0083	0.8519
rs4929947	g	-0.0266	0.0085	0.0018

rs543874	a	-0.0819	0.0097	2E-17
rs6009583	c	0.0055	0.0095	0.5607
rs6427782	a	0.0060	0.0084	0.4725
rs652260	t	0.0040	0.0083	0.6327
rs6555855	g	0.0092	0.0101	0.3608
rs6563739	g	-0.0193	0.0086	0.0254
rs6747380	a	-0.0136	0.0105	0.1951
rs6758290	t	0.0010	0.0085	0.9084
rs6762477	g	0.0210	0.0084	0.0126
rs6770162	a	0.0102	0.0086	0.2336
rs6933660	c	-0.0076	0.0089	0.3925
rs6938574	t	-0.0242	0.0134	0.0710
rs6964833	t	-0.0231	0.0092	0.0117
rs7037266	a	-0.0227	0.0086	0.0080
rs7103411	c	-0.0512	0.0095	8E-08
rs7104764	g	0.0088	0.0096	0.3552
rs7138803	g	-0.0685	0.0079	5E-18
rs7141210	t	0.0063	0.0087	0.4692
rs7215990	g	-0.0112	0.0101	0.2660
rs7463166	a	-0.0244	0.0086	0.0044
rs7514705	c	-0.0522	0.0082	2E-10
rs7642134	g	-0.0057	0.0084	0.4942
rs7647973	a	0.0041	0.0096	0.6671
rs7701886	a	-0.0360	0.0084	2E-05
rs7759938	c	-0.0096	0.0086	0.2632
rs7821178	c	-0.0003	0.0089	0.9732
rs7828501	g	0.0095	0.0084	0.2589
rs7853970	t	-0.0314	0.0087	0.0003
rs7865468	a	0.0019	0.0089	0.8287
rs7955374	t	-0.0205	0.0129	0.1110

rs8032675	t	-0.0256	0.0084	0.0023
rs8050136	c	-0.0694	0.0078	8E-19
rs852069	g	-0.0023	0.0085	0.7908
rs889122	g	-0.0179	0.0091	0.0498
rs900400	t	0.0185	0.0085	0.0306
rs913588	g	0.0025	0.0082	0.7610
rs929843	a	-0.0165	0.0112	0.1433
rs9321659	a	0.0071	0.0124	0.5679
rs939317	g	-0.0115	0.0095	0.2289
rs9447700	c	0.0218	0.0088	0.0140
rs9475752	c	-0.0280	0.0113	0.0130
rs951366	t	-0.0020	0.0084	0.8140
rs9560113	g	-0.0014	0.0093	0.8808
rs9635759	a	0.0017	0.0094	0.8544
rs9647570	g	0.0207	0.0119	0.0817
rs9849248	c	-0.0303	0.0113	0.0072
rs988913	c	-0.0062	0.0086	0.4668

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